REMARKS

Status of the Claims.

Claims 32, 35-47, and 103-104 are pending with entry of this amendment, claims 1-31, 33-34, and 48-102 being cancelled and claims 103 and 104 being added herein. Claims 32, 36, 37, 38, 39, and 40 are amended herein. These amendments introduce no new matter. Support is replete throughout the specification (*e.g.,* page 69, lines 8-9, page 73, lines 16-17, page 73, lines 27-30, in the claims as filed, and so forth).

Election/Restriction.

Pursuant to a restriction requirement made final, Applicants cancel claims 1-31, 34, and 48-102 with entry of this amendment. Please note, however, that Applicants reserve the right to file subsequent applications claiming the canceled subject matter and the claim cancellations should not be construed as abandonment or agreement with the Examiner's position in the Office Action.

Oath/Declaration.

The Examiner alleged that the oath or declaration is defective and requested that a new oath or declaration be provided. A new oath is presently being executed and will be submitted shortly.

Sequence Listing Rules.

A substitute Sequence Listing is provided herewith to comply with sequence rules, 37 C.F.R. §§ 1.821-1.825. A disk containing the sequence(s) in computer readable form, and a paper copy of the sequence information that has been printed from the floppy disk are provided herewith. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy.

Informalities.

The Examiner indicated that the amino acid sequences recited on page 44, lines 9-11 and on page 69, line 4 require sequence identifiers (SEQ ID NOs). The specification is amended on page 44 to insert the required sequence identifiers.

With respect to the recitation of DEVD-AFC on page 69, line 4, Applicants note that **this is a name, not a sequence**, accordingly, no sequence identifier is required.

The Examiner alleged that "B" in SEQ ID NOs:220-230, 232-234, and 240-241 was mis-identified. The "B" in these sequences is correctly identified in the Sequence Listing provided herewith thereby obviating this objection.

The Examiner alleged that the description of Figure 5 was incorrect as stated in paragraph 5 of the Office Action. The description of Figure 5 is amended herein thereby obviating this objection.

The Examiner alleged that the specification indicates the compounds listed in Example 8 (compound structures 2 through 13) at page 67, line 27, but the compounds are not found in the example. The paragraph at page 67, lines 27-31, is amended herein to correctly refer to Example 7 thereby obviating this objection.

The Examiner alleged that the specification, at page 63, indicates the peptide of DAIPNleSIPKGY is called NorFES-KGY, however all the compounds of Table 11 use "NorFES" instead of "NorFES-KGY, and requested correction. For the purposes of consistency, the references to "NorFES-KGY" are amended to refer to "NorFES" as shown in Table 11 thereby obviating this rejection.

Claim Objections.

The Examiner objected to claims 32 and 40 are reciting the nonelected nucleic acid backbone. Claims 32 and 40 are amended herein to eliminate reference to the nucleic acid backbone, thereby obviating this objection.

35 U.S.C. §112, Second Paragraph.

Claims 36-38 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite the recitation of "Fmoc" and "Fa". Claims 36-38 are amended herein to insert the chemical names for "Fmoc" and "Fa" thereby obviating this rejection.

Claims 38 and 39 were rejected for reciting the limitation "said hydrophobic group" in line 1. The Examiner alleged that there is insufficient antecedent basis for this limitation. Claims 38 and 39 are amended herein to depend from claim 35 thereby obviating this rejection.

35 U.S.C. §112, First Paragraph.

Claims 32, 33, and 35-47 were rejected under 35 U.S.C. §112, first paragraph. In particular, the Examiner alleged that the specification was not enabling for a mammalian cell

comprising a fluorogenic composition comprising a polypeptide backbone joining two identical fluorophores, where the fluorophores form an H-type dimmer resulting in the quenching of the fluorescence of the fluorophores, wherein the sequence or the polypeptide and the fluorophores are not defined. Applicants traverse.

The Examiner is respectfully reminded that to be enabling under §112, first paragraph, a patent must contain a description that enables one skilled in the art to make and use the claimed invention. **That some experimentation is necessary does not constitute a lack of enablement**; the amount of experimentation, however, must not be unduly extensive.

Whether undue experimentation is required by one skilled in the art is typically determined by reference to eight factors considered relevant to the inquiry: (1) quantity of experimentation necessary; (2) amount of guidance presented; (3) presence of working examples; (4) nature of the invention; (5) state of the prior art; (6) relative skill of those in the art; (7) predictability of the art; and (8) breadth of the claims. *In re Wands,* 8 USPQ2d 1400 (Fed. Cir. 1988) *citing Ex parte Forman Inc.,* 230 USPQ 546 (BPAI 1986).

Moreover, the Examiner is further reminded that the Federal Circuit Court of Appeals has expressly ruled that screening libraries, *e.g.,* for specific binders is not undue experimentation. *See In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

In the instant case, the specification provides considerable **guidance** (Wands Factor 2) regarding the creation and screening of the "double-labeled" polypeptides of this invention. Thus, for example the specification expressly states:

> Particularly preferred molecules form H-type dimers**. The formation of H-type dimers by fluorescent molecules is described by Packard *et al.* (1996) *Proc. Natl. Acad. Sci. USA*, 93: 11640-11645; Packard *et al.* (1997) *J. Phys. Chem. B*, 101: 5070-5074.** The H-type dimer is characterized by exciton bands in the absorption spectra and fluorescence quenching (*see, e.g.,* Valdes-Aguilera *et al.* (1989) *Acc. Chem. Res.*, 22: 171-177 and Packard *et al.* (1996) *Proc. Natl. Acad. Sci. USA,* 93: 11640-11645). [emphasis added] (page 39, lines 11-16)
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> * * *
>
> **Since blue-shifted exciton bands (or blue-shifted absorption maxima or shoulders) in absorption spectra denote H-dimer formation and fluorescence quenching is concomitant with the latter**, measurement of

> absorption spectra may be sufficient as a diagnostic tool in the proper setting. When a doubly labeled protease indicator is cleaved by a specific protease, the H-type dimer is disrupted. The blue shifted absorption maximum, or shoulders, associated with the H-type dimer is then lost. **Hence, if one measures the intensity of absorption at this blue shifted exciton band then as the H-type dimer is disrupted the absorption intensity is expected to decrease whereas the absorption intensity at the monomer maximum peak wavelength is expected to increase, *i.e.*, the wavelength of the absorption peak is increased or the blue shoulder decreases such that the average wavelength of the band is increased.** [emphasis added] (page 40, lines 7-19)

* * *

> More specifically, spectra of these polypeptides which were doubly labeled with rhodamines **showed a blue-shifted absorption peak and fluorescence quenching, both indicators of H-dimer formation.** [emphasis added] (page 73, lines 13-15)

The specification thus clearly teaches one of skill how to readily identify double labeled polypeptides that participate in H-dimer formation. All that is required is routine screening. Moreover, the Examiner is respectfully reminded that the Court of Appeals for the Federal Circuit has already held that such routine screening **is not** undue experimentation.

Working examples (Wands Factor 3) are provided in the specification. Moreover, Applicants note that Komoriya *et al.* (2000) *J. Exp. Med.*, 191(11): 1819-1828 (attached as Exhibit A) identifies five homo-double labeled polypeptides (protease substrates) made in accordance with the teachings provided herein. Other homo-double labeled polypeptides made in accordance with the teachings provided herein are commercially available from Oncoimmunin, Inc. (*see, e.g.*, OncoImmunin, Inc. (http://www.phiphilux.com/) (*see, e.g.*, profluorescent substrates for Caspase 1 (CaspaLux®-1), Caspase 6 (CaspaLux®-6), Caspase 8 (CaspaLux®-8) and the Caspase 3 Processing Enzyme (CaspaLux®-3PE).

The **nature of the invention** (Wands Factor 4) is relatively straightforward involving only the creation and double labeling of a polypeptide and screening of that molecule for H-dimer formation, as described in the present application. For similar reasons, the **quantity of experimentation** (Wands Factor 1) is not great, and typically routine.

The **state of the prior art** (Wands Factor 1) is well developed with Fluorscent Resonance Energy Transfer (FRET) indicators being well known. Using the teachings provided in the present application, the exploitation of H-dimer formation to permit homo-double labeling of various indicators becomes routine.

With respect to the Examiner's comments regarding the alleged failure of fluorogenic peptides to have sufficient fluorescent quenching (*see* Office Action, page 7, lines 12-17) the Examiner is reminded that, **it is well settled that a claim need not exclude possible inoperable embodiments**. As stated by the PTO Board of Appeals:

> It is always possible to theorize some combination of circumstances which would render a claimed composition or method inoperative, but the art-skilled would assuredly not choose such a combination. *Ex parte* Cole, 223 USPQ 94 (BPAI 1983)

Similarly, the Federal Circuit has stated that

> It is not the function of claims to specifically exclude either possible inoperative substances or ineffective reactant proportions. *In re Dinh-Nguyen and Stenhagen*, 181 USPQ 46 (CCPA 1974)

For a proposed claim to be unpatentable, the law requires that the number of inoperable embodiments be significant in numbers and **not readily ascertained** by those of skill. *In re Cook and Merigold*, 169 USPQ 298, 301-302 (CCPA, 1971).

In the instant case, **inoperable embodiments, are readily identified**, *e.g.* as described and illustrated in the specification. In view of this, the predictability/ascertainability of the art (Wands Factor 7) is relatively good.

The **level of skill** (Wands Factor 6) in the art is high, typically Ph.D.

Finally, with respect to the Examiner's comment that ". . . there are no working examples indicating the make and use of fluorogenic peptides **which do not contain the protease binding site**, nor demonstrating how these peptides are cleaved to produce the fluorescent intensity", the Examiner is reminded that **cleavage of the polypeptide backbone** need not be necessary to produce a fluorescent signal.

As expressly stated in the specification, **fluorescence can also be produce by a change in conformation of the polypeptide backbone** (*e.g.* upon binding a target receptor, nucleic acid, etc.). Thus, for example, the specification states:

> The method involves providing a macromolecule having attached thereto two fluorophores of the same species where the fluorophores form an H-dimer resulting in quenching of fluorescence of the fluorophores; and **detecting a change in fluorescence or absorbance** of the fluorophores wherein a change in fluorescence or fluorescence **indicates a change in conformation** or cleavage of the macromolecule. [emphasis added] (page 7, lines 4-9)

> The present invention provides for novel reagents **whose fluorescence changes** upon cleavage **or a change in conformation of a backbone.** [emphasis added] (*see, e.g.*, abstract)

Moreover, the specification expressly demonstrates that a change in conformation of the molecules of this invention can produce a fluorescent signal. Thus, Example 4 states:

> Thus, the **effect of denaturing conditions on the fluorescence of the fluorogenic protease indicator in the absence of a protease was determined**. First the change of fluorescence of the indicator of Example 1, as a function of added chaotropic reagent concentration (2M or 8M urea) was measured. **When the fluorogenic protease indicator was denatured with a chaotropic reagent the fluorescence intensity increased** with time to a plateau as the molecule denatured (unfolded). [emphasis added] (page 62, lines 15-20).

In view of this teaching, the **breadth of the claims** (Wands Factor 8) is commensurate with the disclosure.

All of the factors recited in *In re Wands* indicate that the claimed invention requires no undue experimentation. Accordingly, the rejection under 35 U.S.C. §112, first paragraph, should be withdrawn.

35 U.S.C. §102.

Claims 32, 33, 35, 39,41, 42, and 43 were rejected under 35 U.S.C. §102(a) as allegedly anticipated by Packard *et al.* (1996) *Proc. Natl. Acad. Sci.*, 93: 11640-11645.

Applicants note that the cited reference (Packard *et al.*) was published in October 1996, less than one year prior to the February 20, 1997 priority date of the present application. According to MPEP §2132.01:

> Applicant's disclosure of his or her own work within the year before the application filing date cannot be used against him or her under 35 U.S.C. 102(a). In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982) (discussed below). Therefore, where the applicant is one of the co-authors of a publication cited against his or her application, the publication may be removed as a reference by the filing of affidavits made out by the other authors establishing that the relevant portions of the publication originated with, or were obtained from, applicant. Such affidavits are called disclaiming affidavits. Ex parte Hirschler, 110 USPQ 384 (Bd. App. 1952). **The rejection can also be overcome by submission of a specific declaration by the applicant establishing that the article is describing applicant's own work**. In re Katz, 687 F.2d 450, 215 USPQ 14 (CCPA 1982). [emphasis added]

Accordingly, Applicants provide herewith a Declaration in accordance with In re Katz, signed by the inventors of the present application, establishing that the Packard *et al.* article describes Applicants' own work, thereby obviating this rejection.

In view of the foregoing, Applicants believes all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested. Should the Examiner seek to maintain the rejections, Applicants request a telephone interview with the Examiner and the Examiner's supervisor.

If a telephone conference would expedite prosecution of this application, the Examiner is invited to telephone the undersigned at (510) 769-3513.

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Respectfully submitted,

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